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Recombinant DNA Research; Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

Recombinant DNA Research; Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules

AGENCY: National Institutes of Health (NIH), HEW.

ACTION: Publication of physical containment recommendations for large-scale uses of organisms containing recombinant DNA molecules.

SUMMARY: These physical containment recommendations for large-scale uses of organisms containing recombinant DNA molecules are published for public information in accordance with the recommendation of the NIH Recombinant DNA Advisory Committee.

FOR FURTHER INFORMATION CONTACT: Dr. W. Emmett Barkely, Director, Division of Safety, Building 13, Room 2E45, National Institutes of Health, Bethesda, Maryland 20205.

SUPPLEMENTAL INFORMATION: The NIH Guidelines for Research Involving Recombinant DNA Molecules (45 FR 6724, January 29, 1980) specify in Section IV–E–1–b–(3)–(d) that the Director, NIH, is responsible for "authorizing, under procedures specified by the RAC, large-scale experiments (i.e., involving more than 10 liters of culture) for recombinant DNAs that are rigorously characterized and free of harmful sequences."

At its September 6–7, 1979, meeting, the NIH Recombinant DNA Advisory Committee (RAC) adopted (by a vote of 14 in favor, none opposed, and 3 abstentions) procedures to be followed in reviewing such large-scale experiments. These procedures included the submission by the applicant of certain information including "a description of the applicant's laboratory practices, containment equipment, and facilities rlevant to the containment of large volumes of culture."

At its May 21–23, 1979, meeting, the RAC approved (by a vote of 19 in favor, none opposed, and no abstentions) the creation of a working group to "examine physical containment requirements for large-scale experiments and that a document should be prepared."

At its December 6–7, 1979, meeting, the RAC reviewed Draft Physical Containment Guidelines for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules and voted (15 in favor, none opposed, and no abstentions) that additional comments be solicited on the draft standards.

At its March 6–7, 1980, meeting, the RAC reviewed Draft Physical Containment Guidelines for Large-Scale Use of Organisms Containing Recombinant DNA Molecules which had been revised from the earlier draft, based upon comments received. Following considerable discussion at the meeting, a motion was passed (with 16 in favor, 2 opposed, and 1 abstention) that the document be published in the **Federal Register.**

The document which is now published in the **Federal Register** contains changes from that reviewed by the RAC on March 7, 1980, based upon suggestions made at the March 7 meeting. These changes are:—(1) To eliminate what was Section VII–C–6 in the draft reviewed by the RAC on March 7, 1980; Section VII–D–6 which consists of identical text has been retained.—(2) To change the phrase "using a non-debilitated strain of the host organisms used in the research or production process" to "using the organism that will serve as the host for propagating the recombinant DNA molecules" in Section VII–B–2, VII–B–5, VII–C–2, VII–C–5, VII–C–8, VII–D–2, VII–D–5, and VII–D–9.

When earlier drafts of this document had been prepared it was proposed that it might eventually be formally promulgated as Part VII of the NIH Guidelines for Research Involving Recombinant DNA Molecules. It has not in fact been formally adopted as Part VII of the NIH Guidelines. The format has, however, been retained in this *Draft* Part VII. This document, while not formally part of the NIH Guidelines, can serve as a model for those preparing submissions to the NIH under the NIH Guidelines.

The document now published in the **Federal Register** is endorsed by the NIH Division of Safety as physical containment recommendations appropriate for large-scale uses of organisms containing recombinant DNA molecules.

Dated: March 31, 1980.

Donald S. Fredrickson,

Director, National Institutes of Health.

Draft Part VII of the NIH Guidelines for Research Involving Recombinant DNA Molecules

VII. Physical Containment for Large-Scale Uses of Viable Organisms Containing Recombinant DNA Molecules

This part of the NIH Guidelines specifies physical containment guidelines for large-scale (greater than 10 liters of culture) research or production involving viable organisms containing recombinant DNA molecules. It shall apply to all large-scale research or production activities approved by the Director, NIH in accordance with Sections IV–E–2–b–(1)–(e) and IV–E–1–b–(3)–(d) of the NIH Guidelines.

All provisions of the NIH Guidelines shall apply to large-scale research or production activities with the following modifications:

- Part VII shall replace Section II–B when quantities in excess of 10 liters of culture are involved in research or production.
- The institution shall appoint a biological safety officer if it engages in large-scale research or production activities involving viable organisms containing recombinant DNA molecules. The duties of the biological safety officer shall include those specified in Section IV–D–4.
- The institution shall establish and maintain a health surveillance program for personnel engaged in large-scale research or production activities involving viable organisms containing recombinant DNA molecules which require P3 containment at the laboratory scale. The program shall include: preassignment and periodic physical and medical examinations; collection, maintenance and analysis of serum specimens for monitoring serologic changes that may result from the employee's work experience; and provisions for the investigation of any serious, unusual or extended illnesses of employees to determine possible occupational origin.

VII–A. *Selection of Physical Containment Levels.* The selection of the physical containment level required for recombinant DNA research or production involving more than 10 liters of culture is based on the containment guidelines established in Part III of the Guidelines. For purposes of large-scale research or production, three physical containment levels are established. These are referred to as P1–LS, P2–LS, and P3–LS. The P1–LS level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules which require P1 containment at the laboratory scale. The P2–LS level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules which require P2 containment at the laboratory scale. The P3–LS level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules which require P3 containment at the laboratory scale. No provisions

are made for large-scale research or production of viable organisms containing recombinant DNA molecules which require P4 containment at the laboratory scale. If necessary, these requirements will be established on an individual case basis.

VII–B. *P1–LS Level.*

VII–V–1. Cultures of viable organisms containing recombinant DNA molecules shall be handled in a closed system (e.g., closed vessel used for the propagation and growth of cultures) or other primary containment equipment (e.g., biological safety cabinet containing a centrifuge used to process culture fluids) which is designed to reduce the potential for escape of viable organisms. Volumes less than 10 liters may be handled outside of a closed system or other primary containment equipment providing all physical containment requirements specified in Section II–B–1. of the Guidelines are met.

VII–B–2. Culture fluids (except as allowed in VII–B3.) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

VII–B–3. Sample collection from a closed system, the addition of materials to a closed system and the transfer of culture fluids from one closed system to another shall be done in a manner which prevents the release of aerosols or contamination of exposed surfaces.

VII–B–4. Exhaust gases removed from a closed system or other primary containment equipment shall be treated by filters which have efficiencies equivalent to HEPA filters or by other equivalent procedures (e.g., incineration) to prevent the release of viable organisms containing recombinant DNA molecules to the environment.

VII–B–5. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure. A validated sterilization procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

VII–B–6. Emergency plans required by Section IV–D–3–d. shall include methods and procedures for handling large losses of culture on an emergency basis.

VII–C. *P2–LS Level.*

VII–C–1. Cultures of viable organisms containing recombinant DNA molecules shall be handled in a closed system (e.g., closed vessel used for the propagation and growth of cultures) or other primary containment equipment (e.g., Class III biological safety cabinet containing a centrifuge used to process culture fluids) which is designed to prevent the escape of viable organisms. Volumes less than 10 liters may be handled outside of a closed system or other primary containment equipment providing all physical containment requirements specified in Section II–B–2. of the Guidelines are met.

VII–C–2. Culture fluids (except as allowed in VII–C–3.) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

VII–C–3. Sample collection from a closed system, the addition of materials to a closed system, and the transfer of cultures fluids from one closed system to another shall be done in a manner which prevents the release of aerosols or contamination of exposed surfaces.

VII–C–4. Exhaust gases removed from a closed system or other primary containment equipment shall be treated by filters which have efficiencies equivalent to HEPA filters or by other equivalent procedures (e.g. incinereation) to prevent the release of viable organisms containing recombinant DNA molecules to the environment.

VII–C–5. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opended for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure. A validated sterilization procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

VII–C–6. Rotating seals and other mechanical devices directly associated with a closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules shall be designed to prevent leakage or shall be fully enclosed in ventilated housings that are exhasted through filters which have efficiencies equivalent to HEPA filters or through other equivalent treatment devices.

VII–C–7. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules and other primary containment equipment used to contain operations involving viable organisms containing recombinant DNA molecules shall include monitoring or sensing devices that monitor the integrity of containment during operations.

VII–C–8. A closed system used for the propagation and growth of viable organisms containing the recombinant DNA molecules shall be tested for integrity of the containment features using the organism that will serve as the host for propagating recombinant DNA molecules. Testing shall be accomplished prior to the introduction of viable organisms containing recombinant DNA molecues, and following modification or replacement of essential containment features. Procedures and methods used in the testing shall be appropriate for the equipment design and for recovery and demonstration of the test organism. Records of tests and results shall be maintained on file.

VII–C–9. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules shall be permanently identified. This identification shall be used in all records reflecting testing, operation, and maintenance and in all documentation relating to the use of this equipment for research or production activities involving viable organisms containing recombinant DNA molecules.

VII–C–10. The universal biohazard sign shall be posted on each closed system and primary containment equipment when used to contain viable organisms containing recombinant DNA molecules.

VII–C–11. Emergency plans required by Section IV–D–3–d shall include methods and procedures for handling large losses of culture on an emergency basis.

VII–D. *P3–LS Level.*

VII–D–1. Cultures of viable organisms containing recombinant DNA molecules shall be handled in a closed system (e.g., closed vessels used for the propagation and growth of cultures) or other primary containment equipment (e.g., Class III biological safety cabinet containing a centrifuge used to process culture fluids) which is designed to prevent the escape of viable organisms. Volumes less than 10 liters may be handled outside of a closed system providing all physical containment requirements specified in Section II–B–3 of the Guidelines are met.

VII–D–2. Culture fluids (except as allowed in VII–D–3) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organisms that will serve as the host for propagating the recombinant DNA molecules.

VII–D–3. Sample collection from a closed system, the addition of materials to a closed system, and the transfer of culture fluids from one closed system to another shall be done in a manner which prevents the release of aerosols or contamination of exposed surfaces.

VII–D–4. Exhaust gases removed from a closed system or other primary containment equipment shall be treated by filters which have efficiencies equivalent to HEPA filters or by other equivalent procedures (e.g. incineration) to prevent the release of viable organisms containing recombinant DNA molecules to the environment.

VII–D–5. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure. A validated sterilization procedure is one which has been demonstrated to be effective using the organisms that will serve as the host for propagating the recombinant DNA molecules.

VII–D–6. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules shall be operated so that the space above the culture level will be maintained at or slightly below atmospheric pressure.

VII–D–7. Rotating seals and other mechanical devices directly associated with a closed system used to contain viable organisms containing recombinant DNA molecules shall be be designed to prevent leakage or shall be fully enclosed in ventilated housings that are exhausted through filters which have efficiencies equivalent to HEPA filters or through other equivalent treatment devices.

VII–D–8. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules and other primary containment equipment used to contain operations involving viable organisms containing recombinant DNA molecules shall include monitoring or sensing devices that monitor the integrity of containment during operations.

VII–D–9. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules shall be tested for integrity of the containment features using the organisms that will serve as the host for propagating the recombinant DNA molecules. Testing shall be accomplished prior to the introduction of viable organisms containing recombinant DNA molecules, and following modification or replacement of essential containment features. Procedures and methods used in the testing shall be appropriate for the equipment design and for recovery and demonstration of the test organism. Records of tests and results shall be maintained on file.

VII–D–10. A closed system used for the propagation and growth of viable organisms containing recombinant DNA molecules shall be permanently identified: This identification shall be used in all records reflecting testing, operation and maintenance and in all documentation relating to the use of this equipment for research or production activities involving viable organisms containing recombinant DNA molecules.

VII–D–11. The universal biohazard sign shall be posted on each closed system and primary containment equipment when used to contain viable organisms containing recombinant DNA molecules.

VII–D–12. Emergency plans required by Section IV–D–3–d shall include methods and procedures for handling large losses of culture on an emergency basis.

VII–D–13. Closed systems and other primary containment equipment used in handling cultures of viable organisms containing recombinant DNA molecules shall be located within a controlled area which meets the following requirements:

VII–D–13–a. The controlled area shall have a separate entry area. The entry area shall be a double-doored space such as an air lock, anteroom or change room that separates the controlled area from the balance of the facility.

VII–D–13–b. The surfaces of walls, ceilings, and floors in the controlled area shall be such as to permit ready cleaning and decontamination.

VII–D–13–c. Penetrations into the controlled area shall be sealed to permit liquid or vapor phase space decontamination.

VII–D–13–d. All utilities and service or process piping and wiring entering the controlled area shall be protected against contamination.

VII–D–13–e. Handwashing facilities equipped with foot-, elbow-, or automatically-operated valves shall be located at each major work area and near each primary exit.

VII–D–13–f. A shower facility shall be provided. This facility shall be located in close proximity to the controlled area.

VII–D–13–g. The controlled area shall be designed to preclude release of culture fluids outside the controlled area in the event of an accidental spill or release from the closed systems or other primary containment equipment.

VII–D–13–h. The controlled area shall have a ventilation system that is capable of controlling air movement. The movement of air shall be from areas of lower contamination potential to areas of higher contamination potential. If the ventilation system provides positive pressure supply air, the system shall operate in a manner that prevents the reversal of the direction of air movement or shall be equipped with an alarm that would be actuated in the event that reversal in the direction of air movement were to occur. The exhaust air from the controlled area shall not be recirculated to other areas of the facility. The exhaust air from the controlled area may be discharged to the outdoors without filtration or other means for effectively reducing an accidental aerosol burden provided that it can be dispersed clear of occupied buildings and air intakes.

VII–D–14. The following personnel and operational practices shall be required:

VII–D–14–a. Personnel entry into the controlled area shall be through the entry area specified in section VII–D–13–a.

VII–D–14–b. Persons entering the controlled area shall exchange or cover their personal clothing with work garments such as jumpsuits, laboratory coats, pants and shirts, head cover, and shoes or shoe covers. On exit from the controlled area the work clothing may be stored in a locker separate from that used for personal clothing or discarded for laundering. Clothing shall be decontaminated before laundering.

VII–D–14–c. Entry into the controlled area during periods when work is in progress shall be restricted to those persons required to meet program or support needs. Prior to entry all persons shall be informed of the operating practices, emergency procedures, and the nature of the work conducted.

VII–D–14–d. Persons under 18 years of age shall not be permitted to enter the controlled area.

VII–D–14–e. The universal biohazard sign shall be posted on entry doors to the controlled area and all internal doors when any work involving the organism is in progress. This includes periods when decontamination

procedures are in progress. The sign posted on the entry doors to the controlled area shall include a statement of agents in use and personnel authorized to enter the controlled area.

VII–D–14–f. The controlled area shall be kept neat and clean.

VII–D–14–g. Eating, drinking, smoking and storage of food are prohibited in the controlled area.

VII–D–14–h. Animals and plants shall be excluded from the controlled area.

VII–D–14–i. An effective insect and rodent control program shall be maintained.

VII–D–14–j. Access doors to the controlled area shall be kept closed, except as necessary for access, while work is in progress. Service doors leading directly outdoors shall be sealed and locked while work is in progress.

VII–D–14–k. Persons shall wash their hands when leaving the controlled area.

VII–D–14–l. Persons working in the controlled area shall be trained in emergency procedures.

VII–D–14–m. Equipment and materials required for the management of accidents involving viable organisms containing recombinant DNA molecules shall be available in the controlled area.

VII–D–14–n. The Controlled area shall be decontaminated in accordance with established procedures following spills or other accidental release of viable organisms containing recombinant DNA molecules.

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